

EDITORIAL

Clinical & Experimental Allergy

Next stop for HDL: the lung

This editorial discusses the findings of the paper in this issue by P. K. Yiallourous et al. [15], pp. 423–432.

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Although the lung is not widely conceived of as sensitive to circulating lipoprotein particles and their cholesterol cargo, a number of reports over the years have suggested important and perhaps even unique roles for serum lipoproteins in lung biology. Low-density lipoprotein (LDL) is taken up by the lung *in vivo* [1], and it and high density lipoprotein (HDL) stimulate surfactant production by alveolar epithelial type II cells [2] and growth of lung fibroblasts [3]. HDL moreover serves as the major source of the antioxidant vitamin E for alveolar epithelial type II cells [4]. The lungs of HDL-deficient apolipoprotein A-I null mice display increases in oxidative stress, inflammation, collagen deposition and airway hyperresponsiveness [5], and HDL-cholesterol deficiency is also associated with lower lung function in human populations [6]. Conversely, surfactant proteins A and D are potent inhibitors of LDL oxidation [7], an oxidative event that presumably poses a unique challenge for the lung, given its direct exposure to atmospheric oxygen and radicals.

Serum LDL-cholesterol and HDL-cholesterol have well-established epidemiological associations (positive and negative, respectively) with atherosclerotic cardiovascular disease, in which context it is thought that dysregulated cholesterol loading, oxidative stress, inflammation and apoptosis of vascular cells driven by the former is combated by cholesterol removal and antioxidant, anti-inflammatory, and anti-apoptotic actions of the latter. Upon this backdrop, interest has also recently arisen in

whether serum lipoproteins impact human lung disease. Several studies have now examined the relationship between serum cholesterol measures and asthma [8–14]. Many of these have been cross-sectional or retrospective analyses and some are limited by virtue of having examined only total cholesterol, a value comprised by both HDL- and LDL- (as well as other apolipoprotein B-containing lipoproteins) cholesterol fractions. Collectively, a variety of relationships have been reported between cholesterol measures and asthma, including no association for either LDL- or HDL-cholesterol [9, 13], a positive association for total cholesterol [8], positive for HDL-cholesterol and inverse for total cholesterol [10], positive for HDL-cholesterol [11], negative for HDL-cholesterol [14], and no association for HDL-cholesterol, but a negative association for total- and non-HDL-cholesterol [12].

To this, we must now add a new study by Yiallourous and colleagues that appears in this issue of the journal [15]. The authors report that low HDL-cholesterol at age 11–12 years was associated with diagnoses of ever asthma and active asthma at age 15–17 years among 3982 Cypriot children. This association persisted after adjustment for body mass index and physical fitness. No association with asthma was found for either total cholesterol or LDL-cholesterol. The analysis is both strengthened and limited by the narrow demographics of the study population. The longitudinal design and large size of the study population are clear strengths of the report.

How may we reconcile the disparate results across studies? At least some of the divergence may possibly arise from the wide range of age and racial/ethnic background of the study populations across these published studies. In addition to probable differences in both lipoprotein and asthma biology in different age groups, genetic background may be critical. It may also be overly simplistic to expect HDL and other lipoproteins to have the same relationship with all subphenotypes of asthma, as lipoproteins may conceivably impact 'asthma' pathogenesis independently at multiple levels, including the pathway to atopy, the pathway from atopy to lung

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disease, and the pathway to non-atopic airway disease. Moreover, oxidized lipoprotein species (e.g. oxidized LDL), levels of which were not measured in these studies, have distinct biological effects from native lipoproteins. Whether lipoproteins are even causal in the asthma phenotype is also open to question, as it is possible that other disorders of the metabolic syndrome with which dyslipidaemia variably clusters, such as insulin resistance, may possibly drive the apparent relationship to asthma. Finally, cross-sectional studies also carry the risk of reverse causation, an issue that may be a real concern insofar as lipoprotein levels are known to be affected by the acute phase response.

As we consider the heterogeneity of studies of the lipoprotein–asthma relationship, it is also critical to reflect upon the complex and heterogeneous composition of lipoproteins themselves. Serum lipoproteins are multi-molecular complexes of lipids and proteins. HDL is thought to contain > 40 distinct proteins [16]. The wide range of function of these proteins, which include complement regulation, protease inhibition and acute phase response, underscores the fact that HDL and other lipoproteins serve broader roles in biology than just transport of cholesterol and other lipids in the circulation. Indeed, HDL particles have potent anti-inflammatory, anti-apoptotic, antioxidant and anti-microbial functions [16], and even play a critical role in adrenal glucocorticoid synthesis [17]. Further complicating matters, HDL particles are themselves not a uniform population, but are composed of several discrete subspecies that have been variably categorized by density and electrophoretic pattern.

Taken in this light, it is critical to remember that HDL-cholesterol (i.e. the cholesterol content of HDL), although perhaps the easiest, oldest and most widespread metric applied to HDL, is neither synonymous with, nor an all-encompassing summary measure of, HDL. This has been reinforced by recent studies showing that HDL-cholesterol levels account for only a small portion of the variation across human subjects in the capacity of serum to induce cholesterol efflux from cells (i.e. HDL function), and that the relationship of serum cholesterol efflux capacity to atherosclerotic disease is independent of HDL-cholesterol [18]. Moreover, failures of HDL-cholesterol-raising agents to improve cardiovascular disease outcomes in recent trials (ILLUMINATE, AIM-HIGH) have even challenged the paradigm of HDL-cholesterol *per se* as atheroprotective. It has been increasingly recognized that not only can the anti-inflammatory and cholesterol-mobilizing functions of HDL be impaired by oxidation of HDL-associated proteins (e.g. apolipoprotein A-I), thereby dissociating HDL function from HDL quantity, but dysfunctional HDL can itself even be pro-inflammatory. With all this has come the realization that more sophisticated measures of HDL *quality* need to be developed that can be applied at a population level.

While there is still value in continuing to examine the relationship of lipoprotein cholesterol levels to asthma, future studies will likely need to phenotype asthma and metabolic status of study subjects very carefully, and to follow the lead of the cardiovascular sciences as more precise and informative measures are applied to serum lipoproteins. While several studies have suggested that the relationship of lipoprotein cholesterol to asthma is independent of obesity, it will nonetheless be interesting to examine how much of the obesity–asthma relationship is dependent upon and/or modified by dyslipidaemia. It will also be valuable to consider that some HDL cargo may aggravate asthma in the face of other HDL cargo that is protective. A possible example of the former is the HDL-associated lipid sphingosine-1-phosphate, which has been reported to exacerbate asthma phenotypes in mice [19].

As we consider directions for future study of lipoprotein–asthma relationships, emerging research has already begun to indicate some promise for lipoprotein-modifying agents in asthma therapy. Apolipoprotein A-I mimetics, peptides that recapitulate the structure and anti-inflammatory function of the HDL-associated protein apolipoprotein A-I, are under study as cardiovascular disease therapeutics in early human trials. Of interest, they have recently been shown to ameliorate disease measures in rodent models of atopic asthma [20, 21]. Hydroxy-methylglutaryl-coenzyme A reductase inhibitors (i.e. ‘statins’), long used in the treatment of dyslipidaemia and atherosclerotic cardiovascular disease, not only reduce serum LDL-cholesterol and triglycerides, but also elevate serum HDL-cholesterol. Statins also have more pleiotropic immunomodulatory actions that stem in part from their depletion of cellular isoprenoids. While rodent model studies indicate that statins improve allergic asthma measures, early trials of statins in human asthma have so far yielded more mixed results [22], suggesting that further study is warranted.

In sum, the study of serum lipoproteins in asthma and in lung disease in general clearly holds great promise for expanding our paradigms of lung disease pathogenesis and, potentially, our therapeutic armamentarium. The field of respiratory biology, basic and clinical alike, is well-positioned now to take advantage of past and ongoing lessons learnt by the cardiovascular field, and to apply these as well as cardiovascular reagents and disease models to the lung. A little opportunism between organ systems may possibly end up going a long way.

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